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Zenoni et al.

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(45) **Date of Patent: Aug. 4, 2015**

(54) **PRODRUG OF AN ANTI-INFLAMMATORY ACTIVE INGREDIENT**

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C07C 229/64	(2006.01)
C07C 229/42	(2006.01)

(52) **U.S. Cl.**
CPC ***C07C 227/04*** (2013.01); ***C07C 229/42*** (2013.01); ***C07C 229/64*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Karl J Puttlitz
(74) *Attorney, Agent, or Firm* — Silvia Salvadori, P.C.

(57) **ABSTRACT**

A process for the preparation of a prodrug of 5-aminosalicylic acid, namely 2-butanoyloxy-5-amino-benzoic acid, and solid forms of such compound are described.

1 Claim, 14 Drawing Sheets

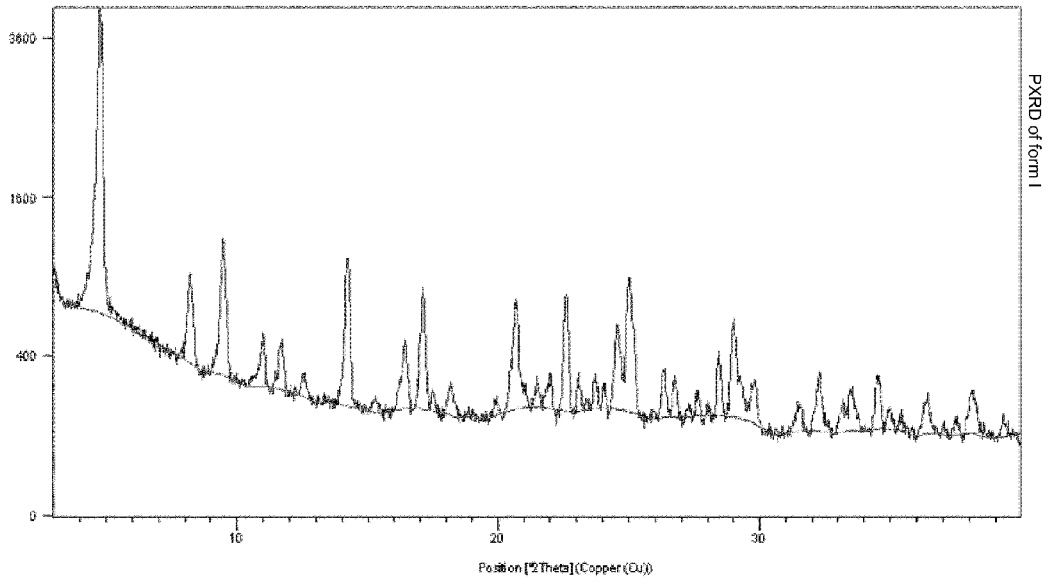


FIGURE 1 – PXRD of form I

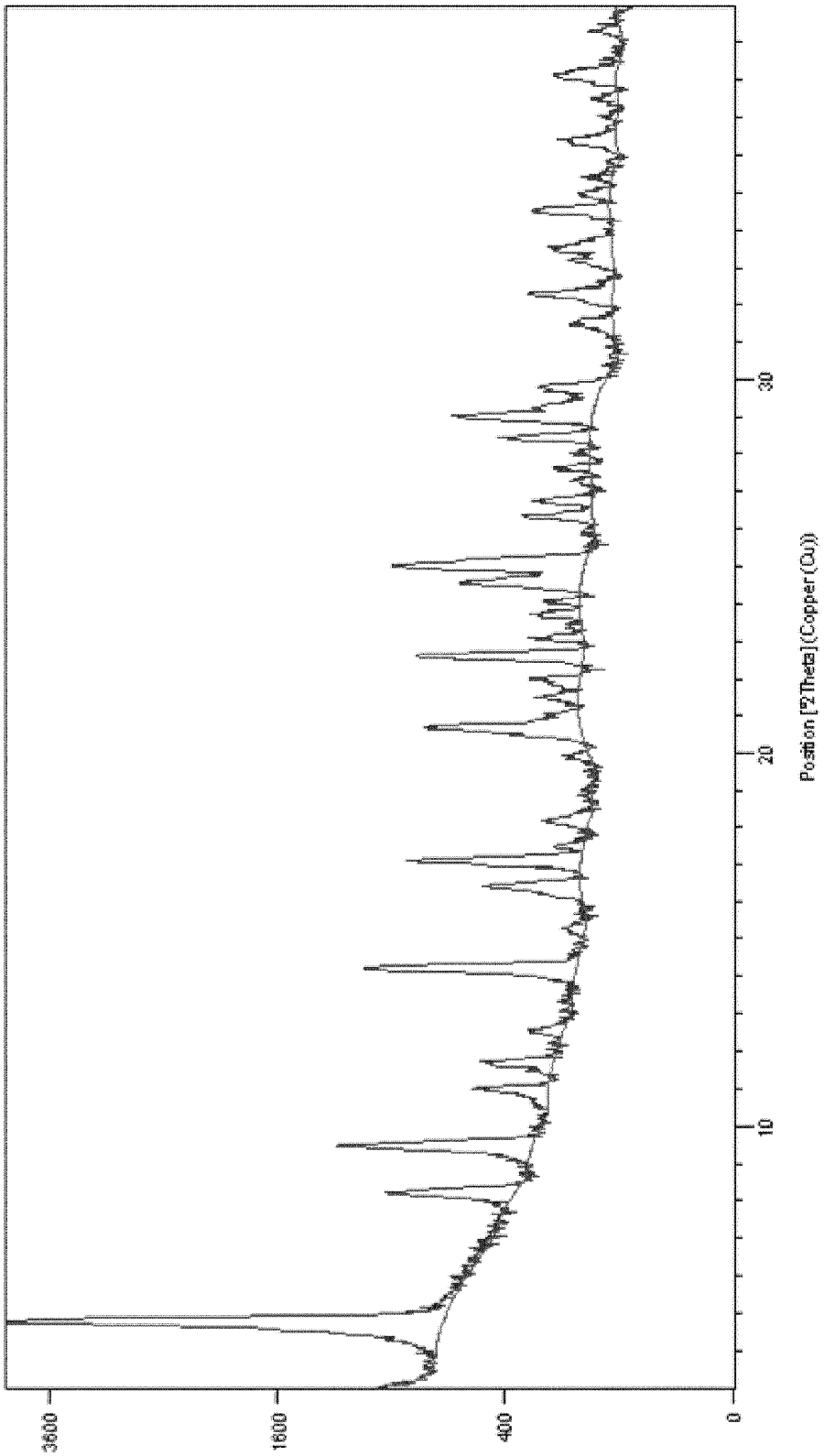


FIGURE 2 – FTIR of form I

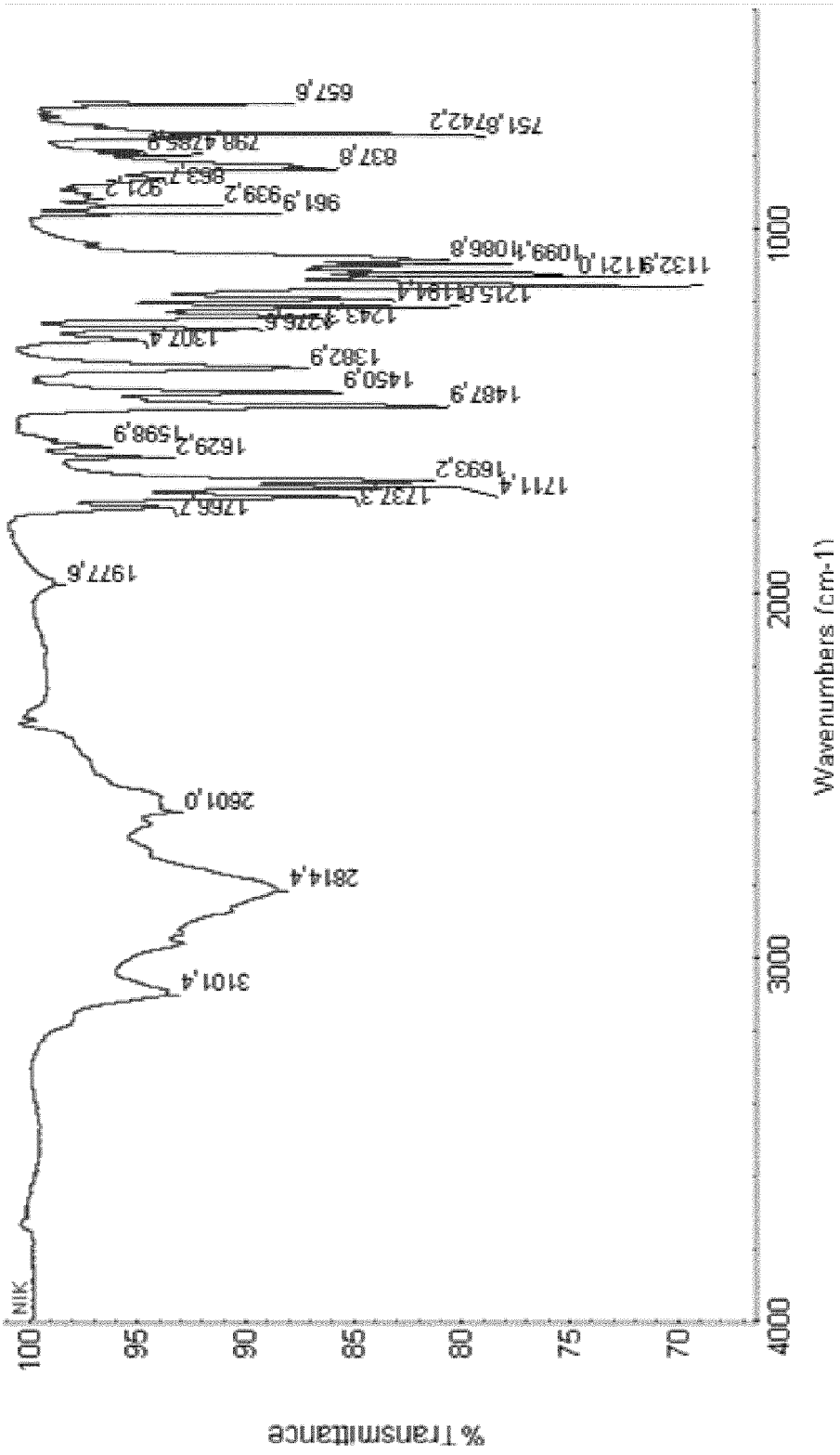


FIGURE 3 – DSC of form I

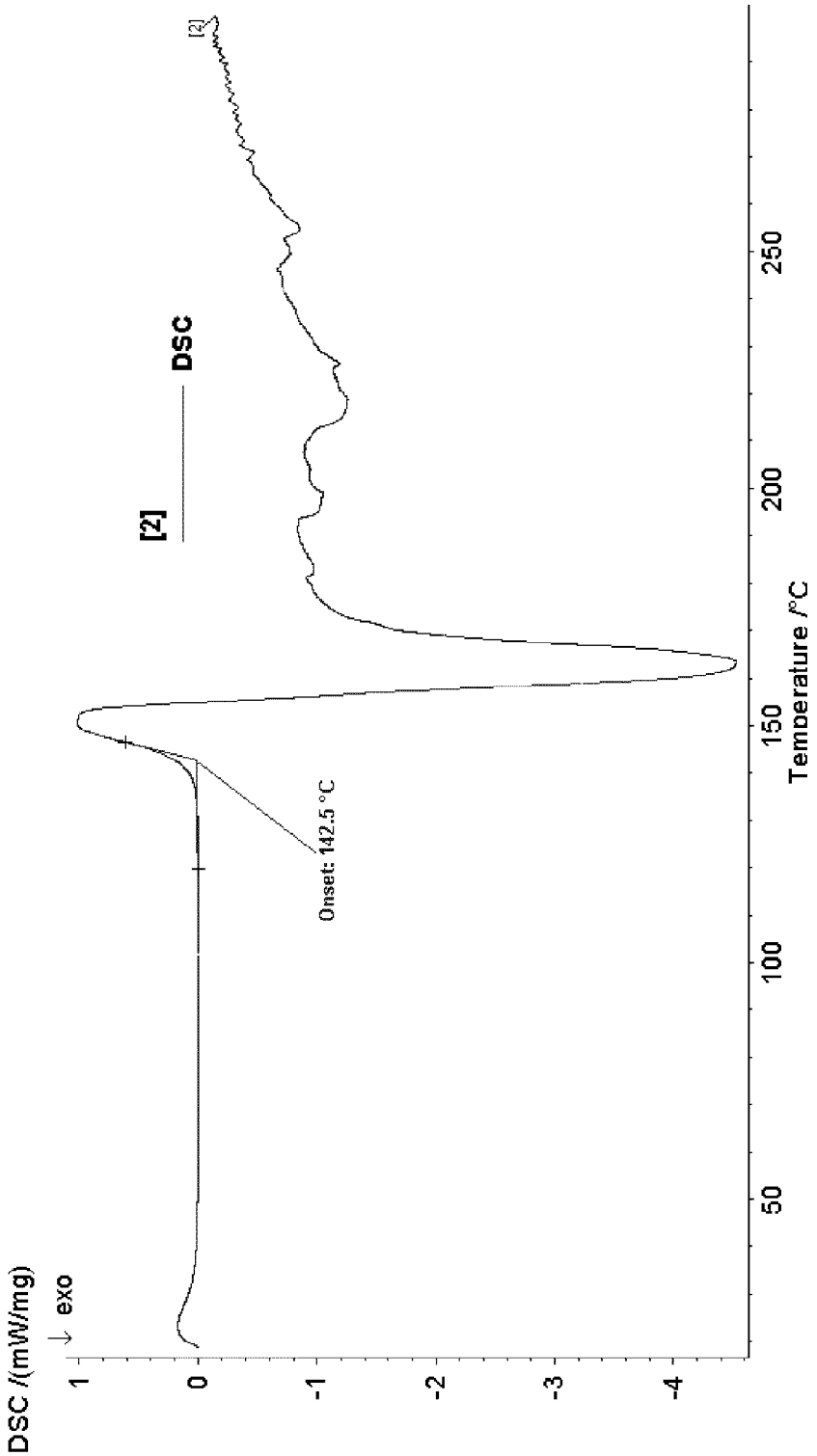


FIGURE 4 – TGA of form I

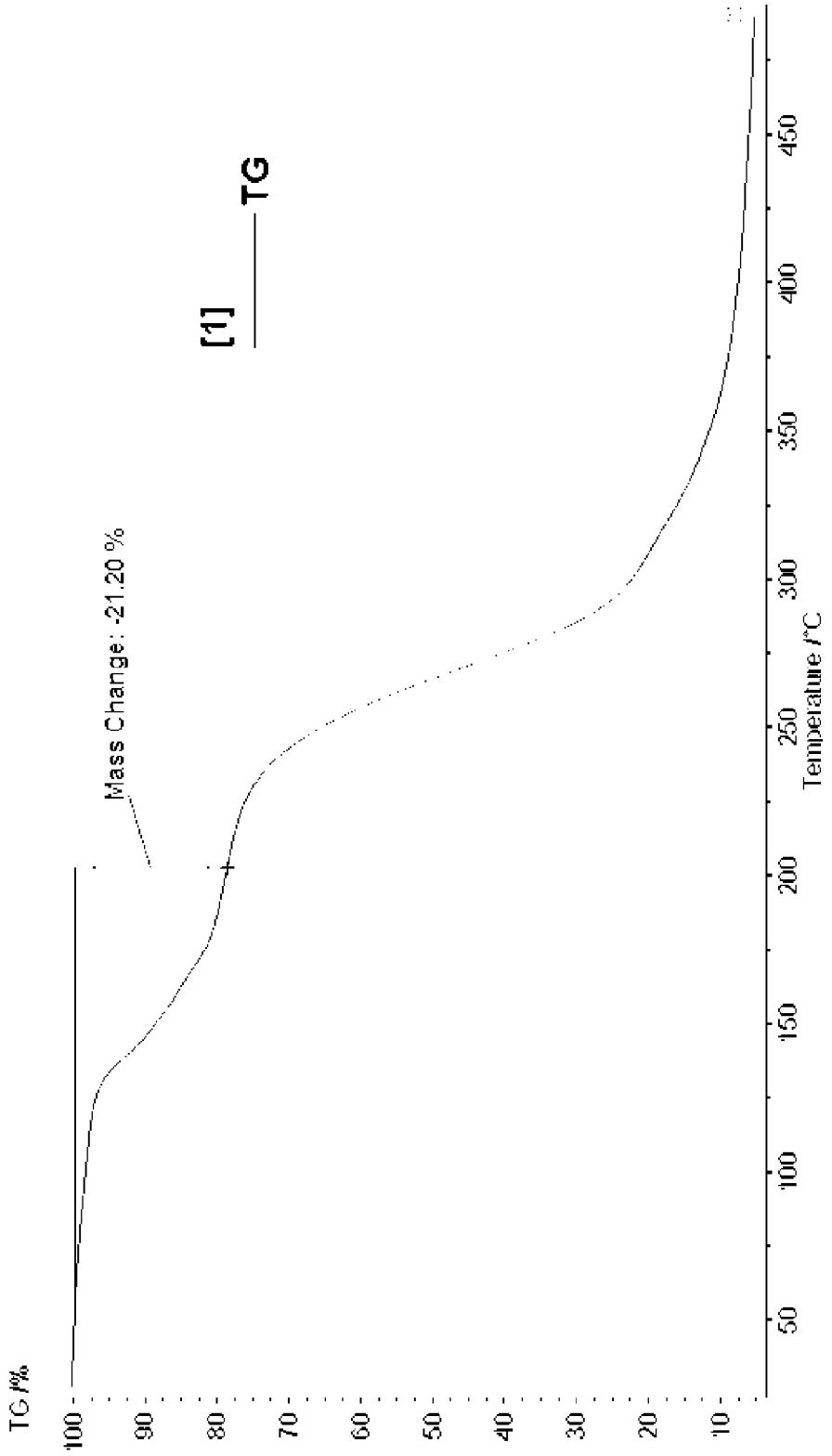


FIGURE 5 – PXRD of form II

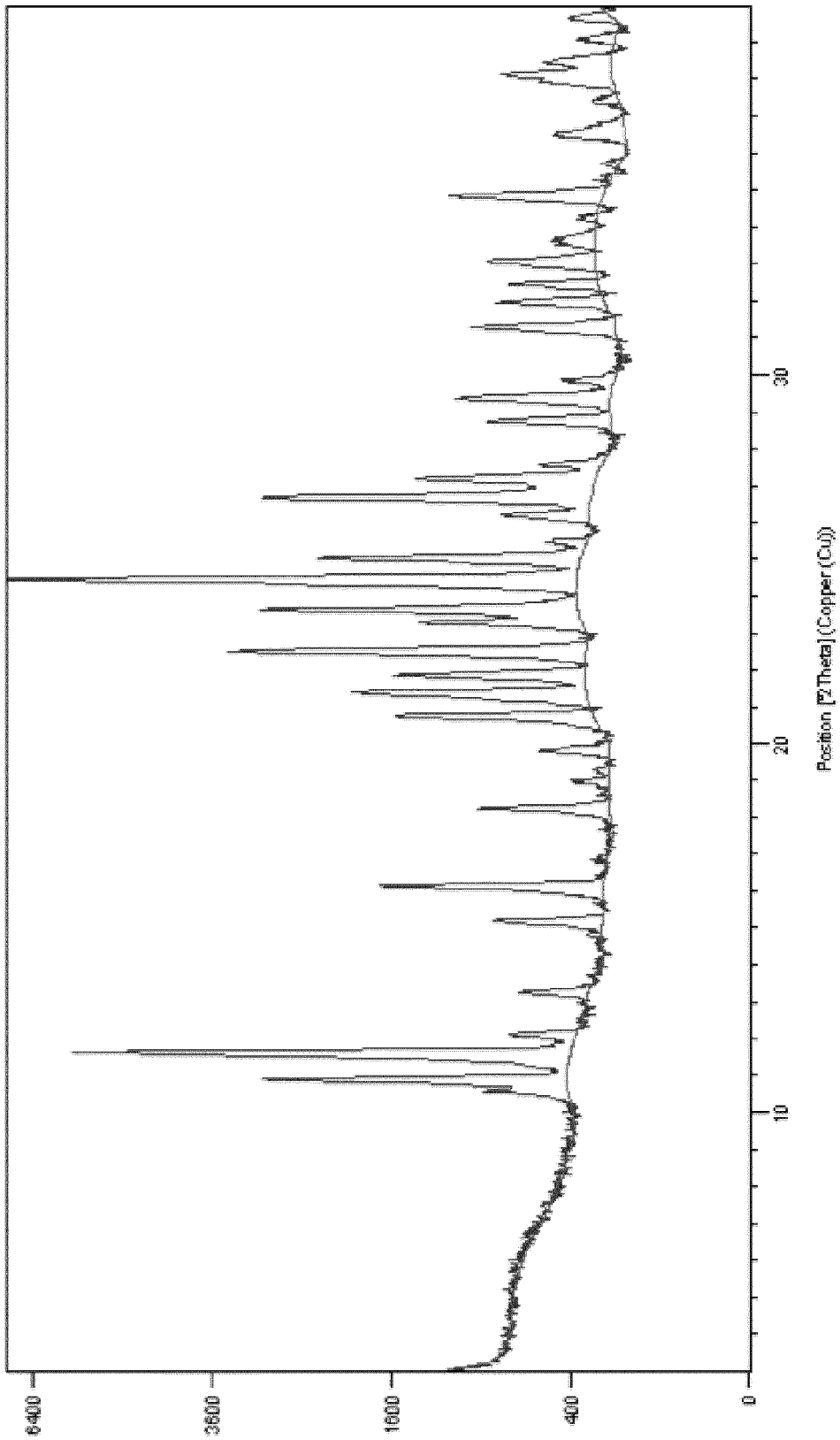


FIGURE 6 – FTIR of form II

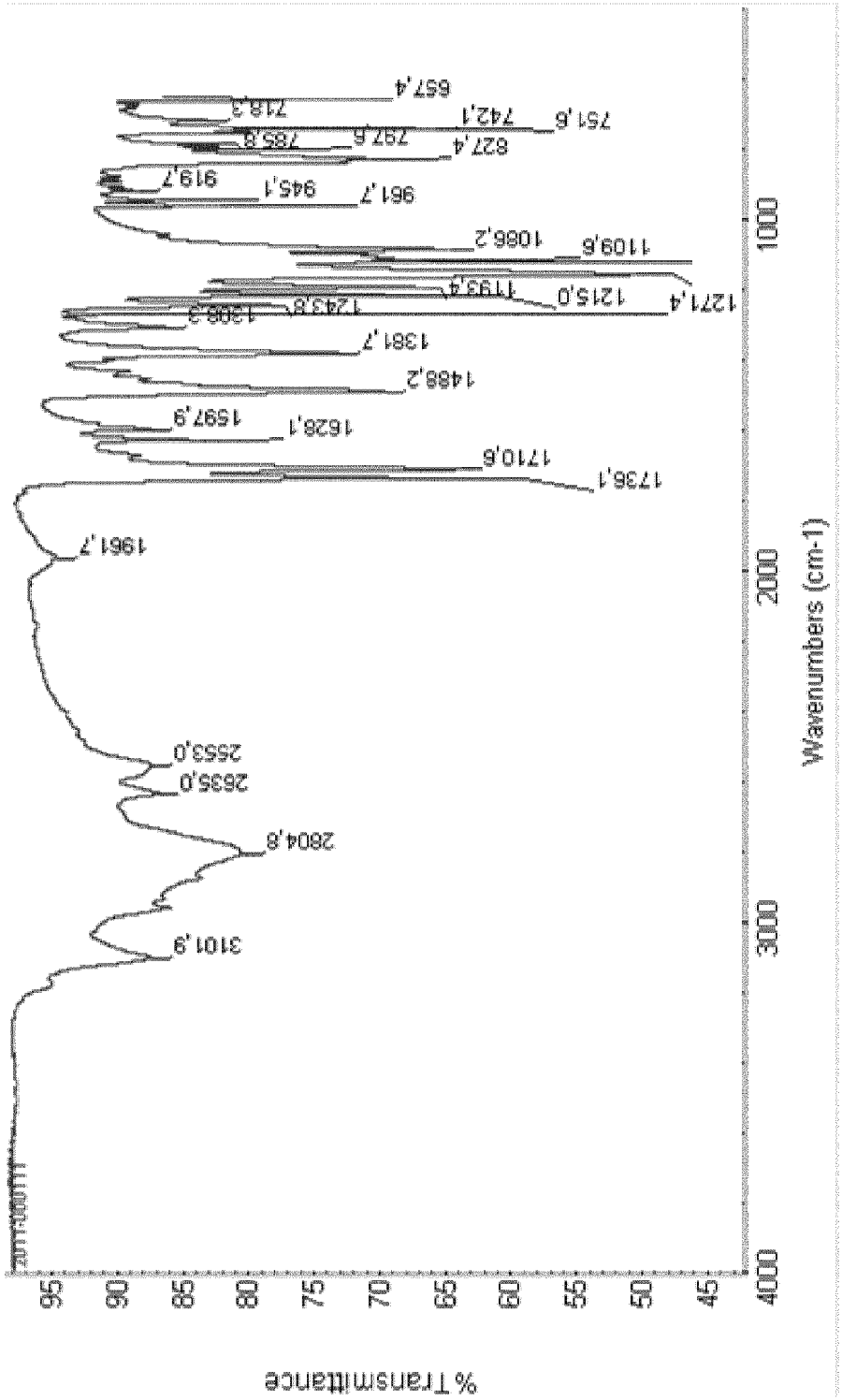


FIGURE 7 – DSC of form II

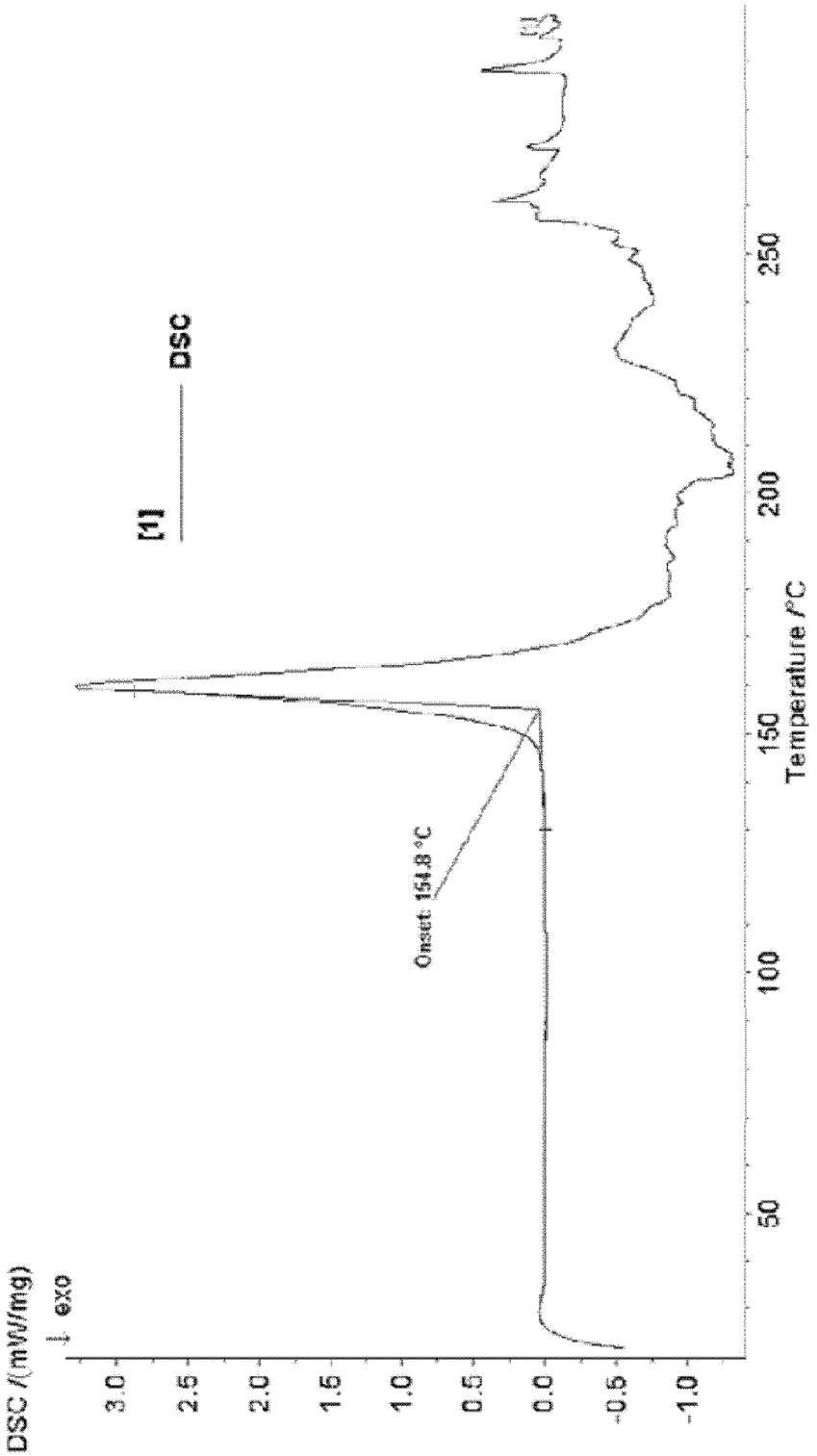


FIGURE 8 – TGA of form II

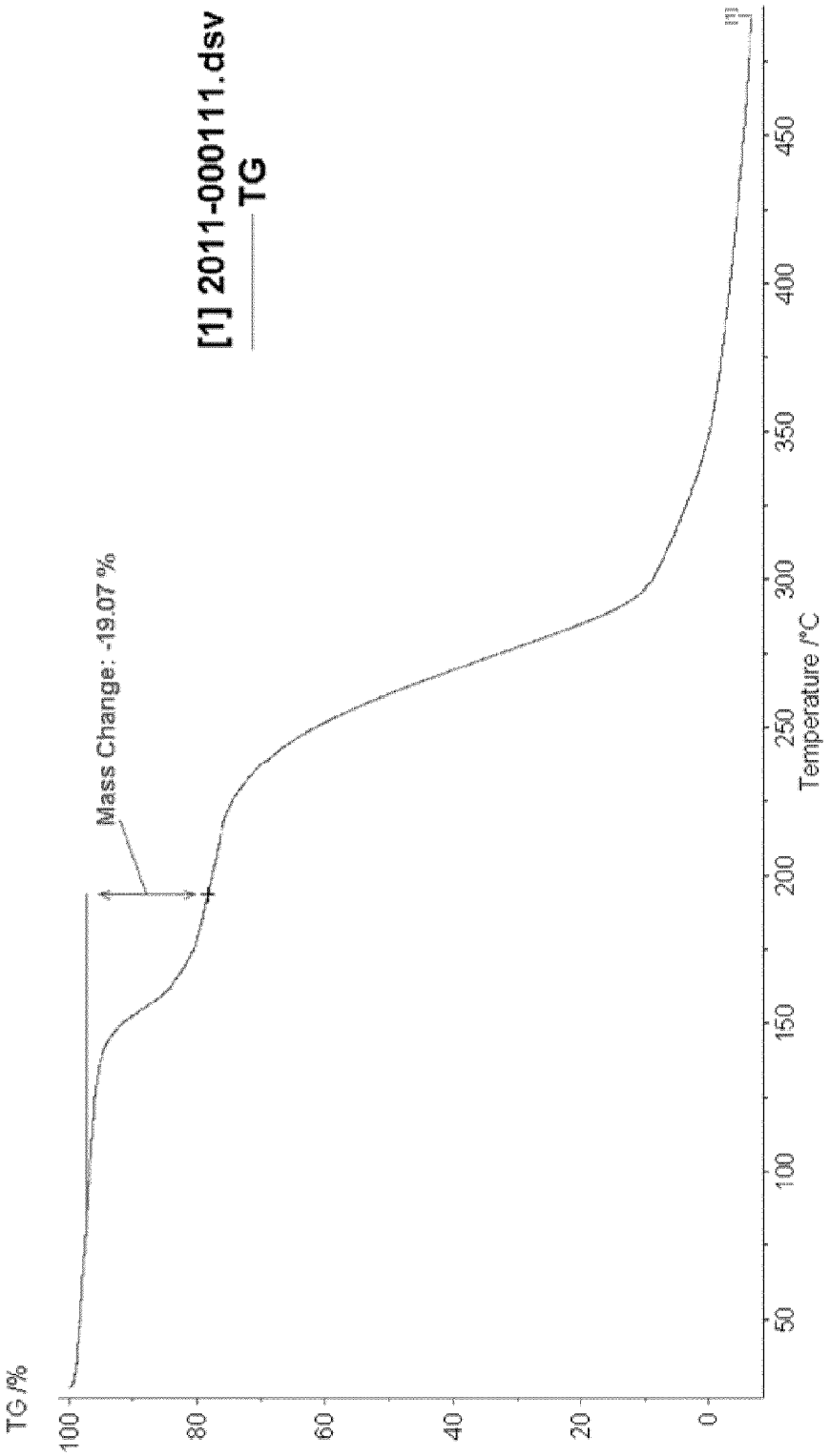


FIGURE 9 – PXRD of form III

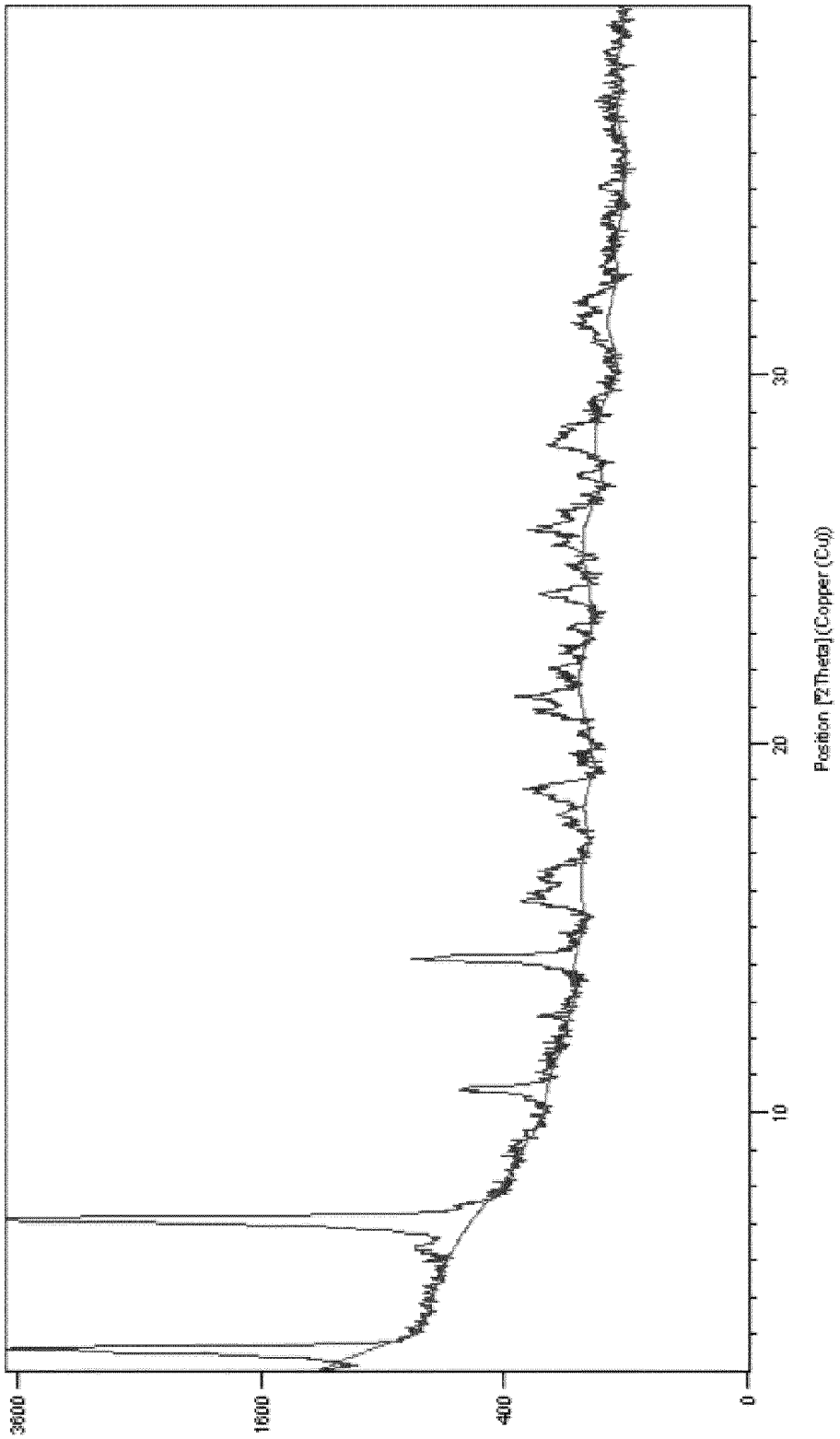


FIGURE 10 – FTIR of form III

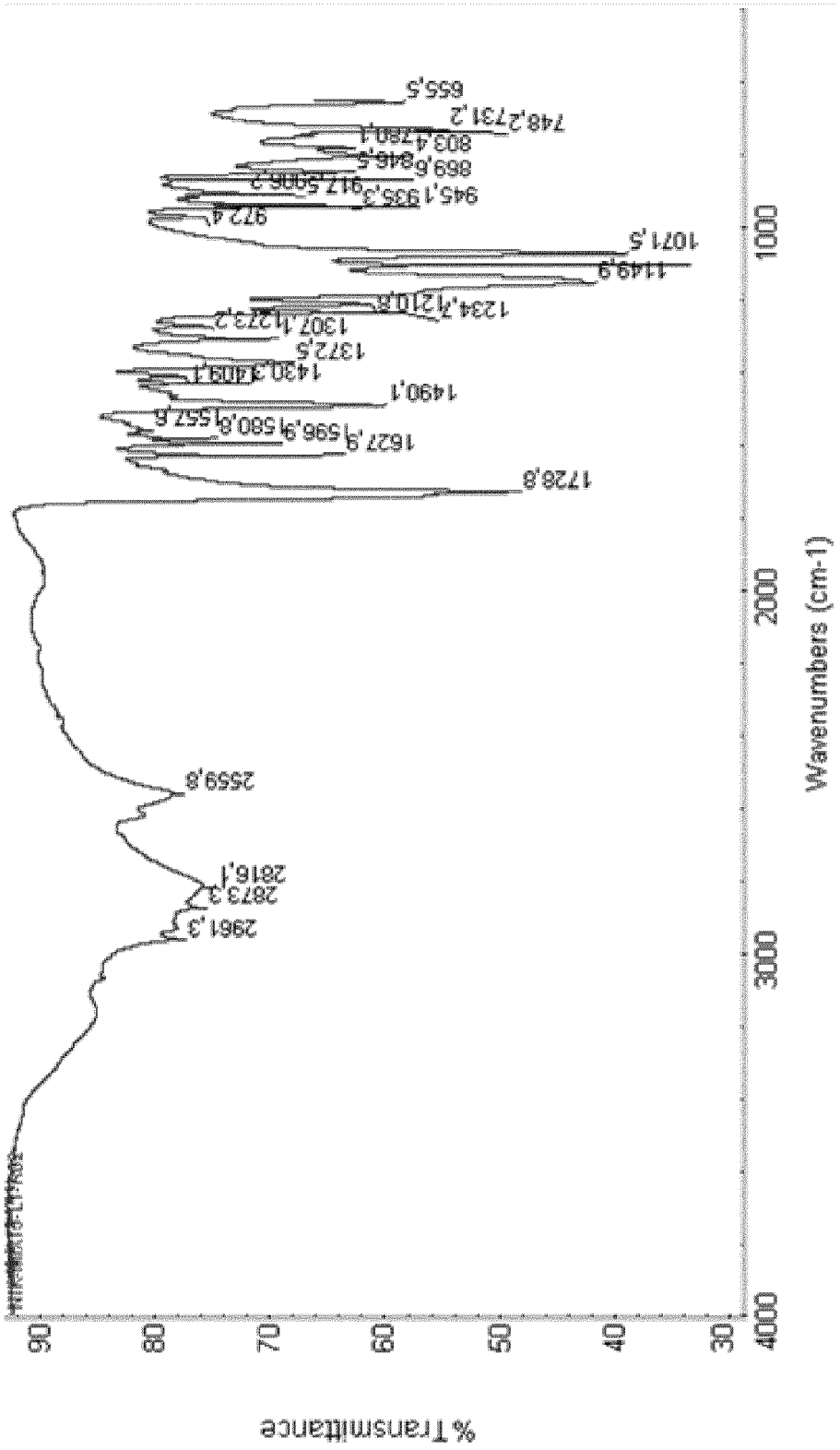


FIGURE 11 – DSC of form III

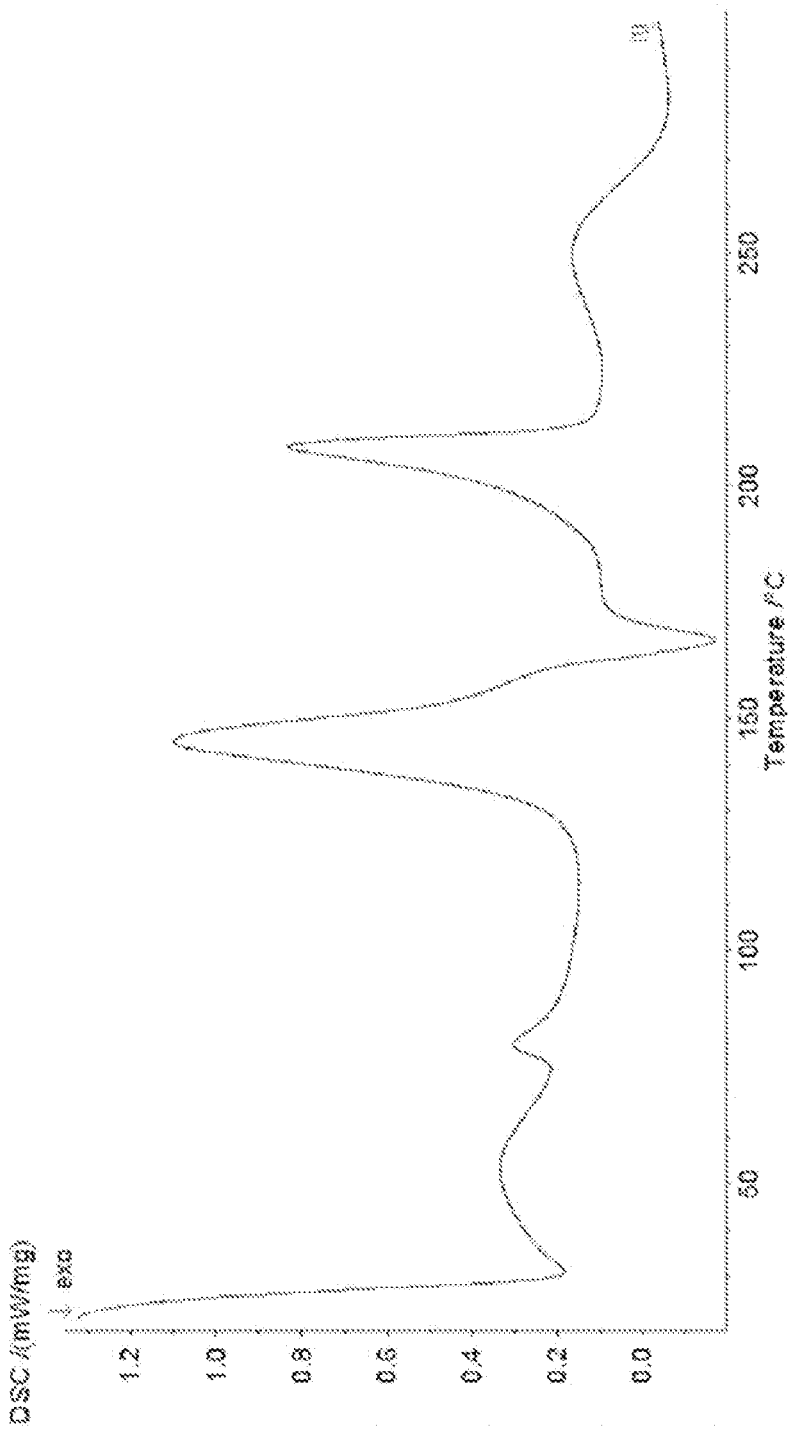


FIGURE 12 – TGA of form III

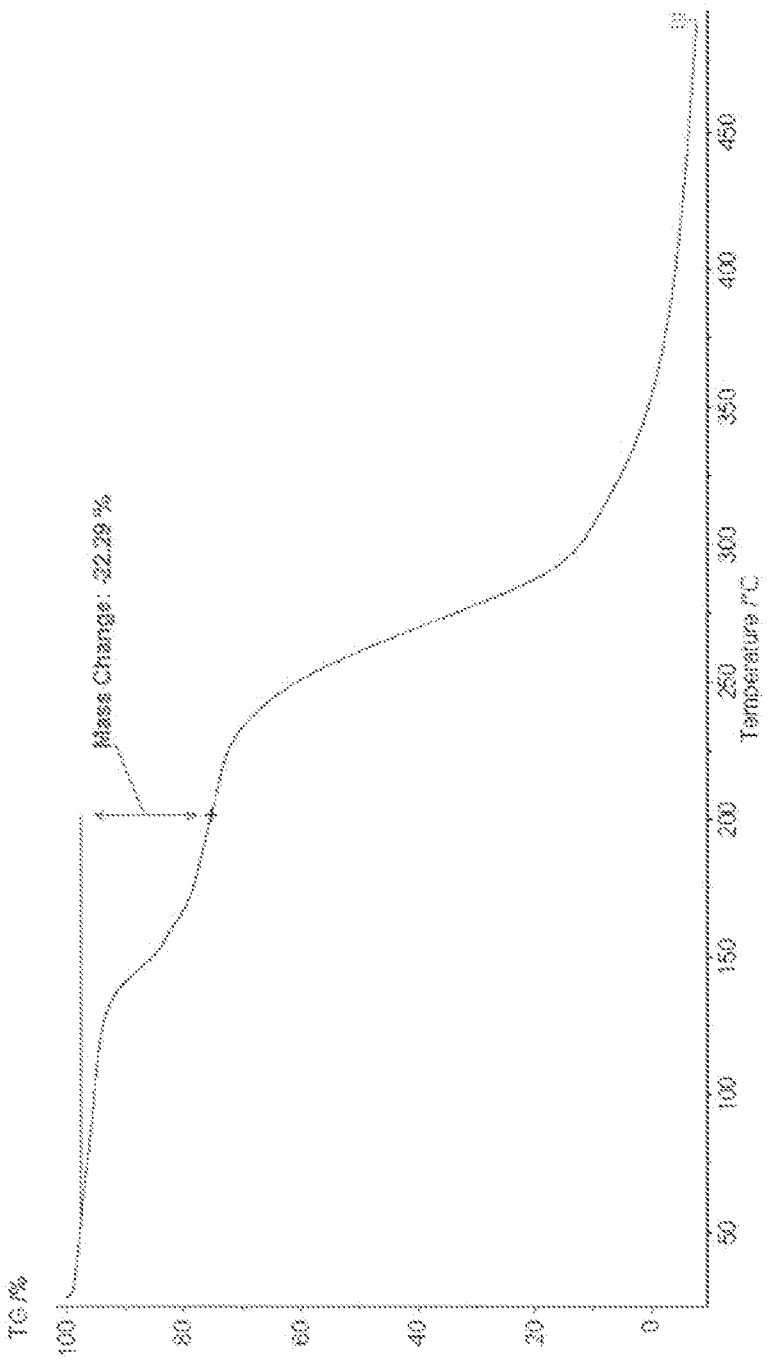


FIGURE 13 – PXRD of amorphous form

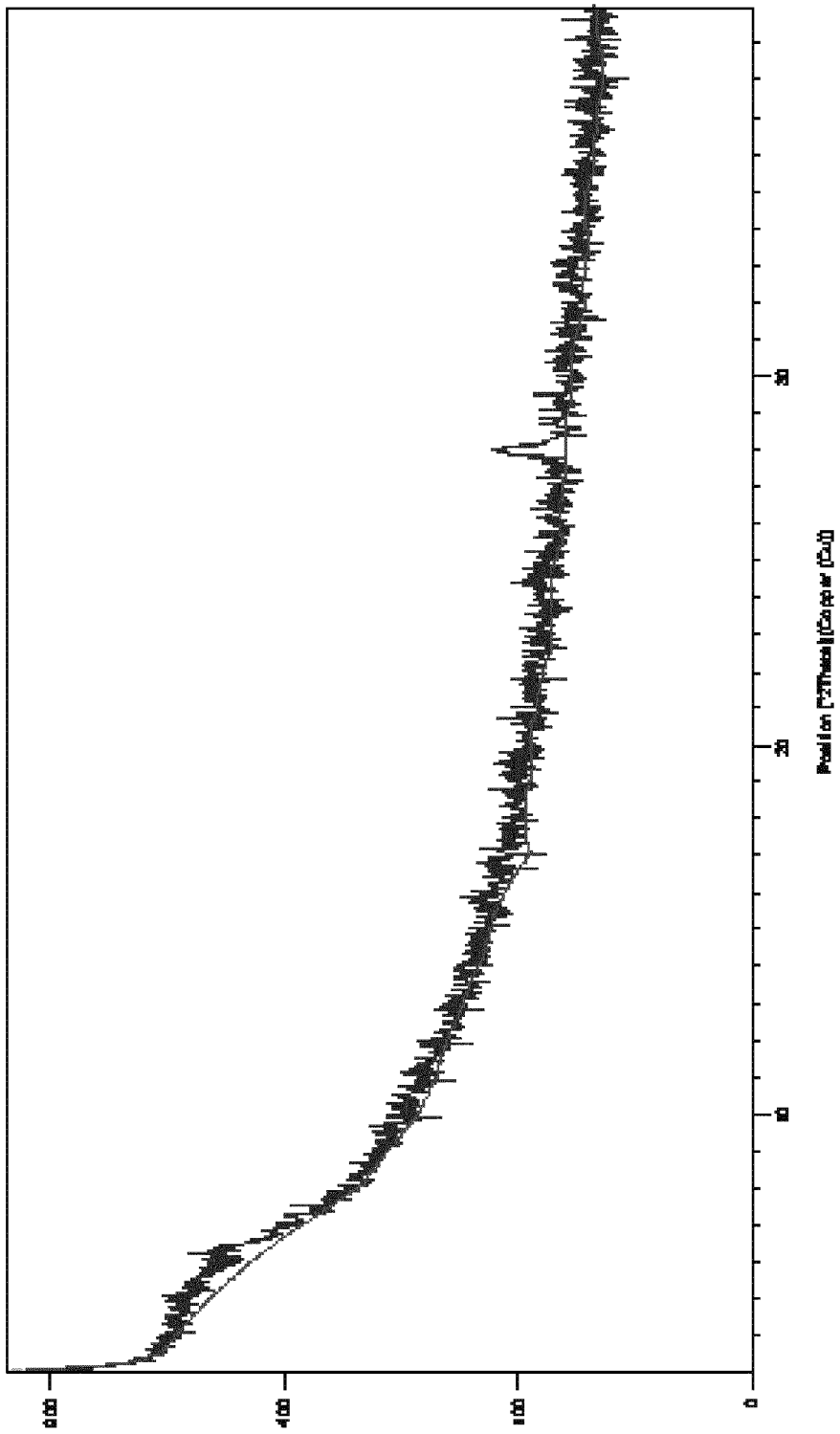
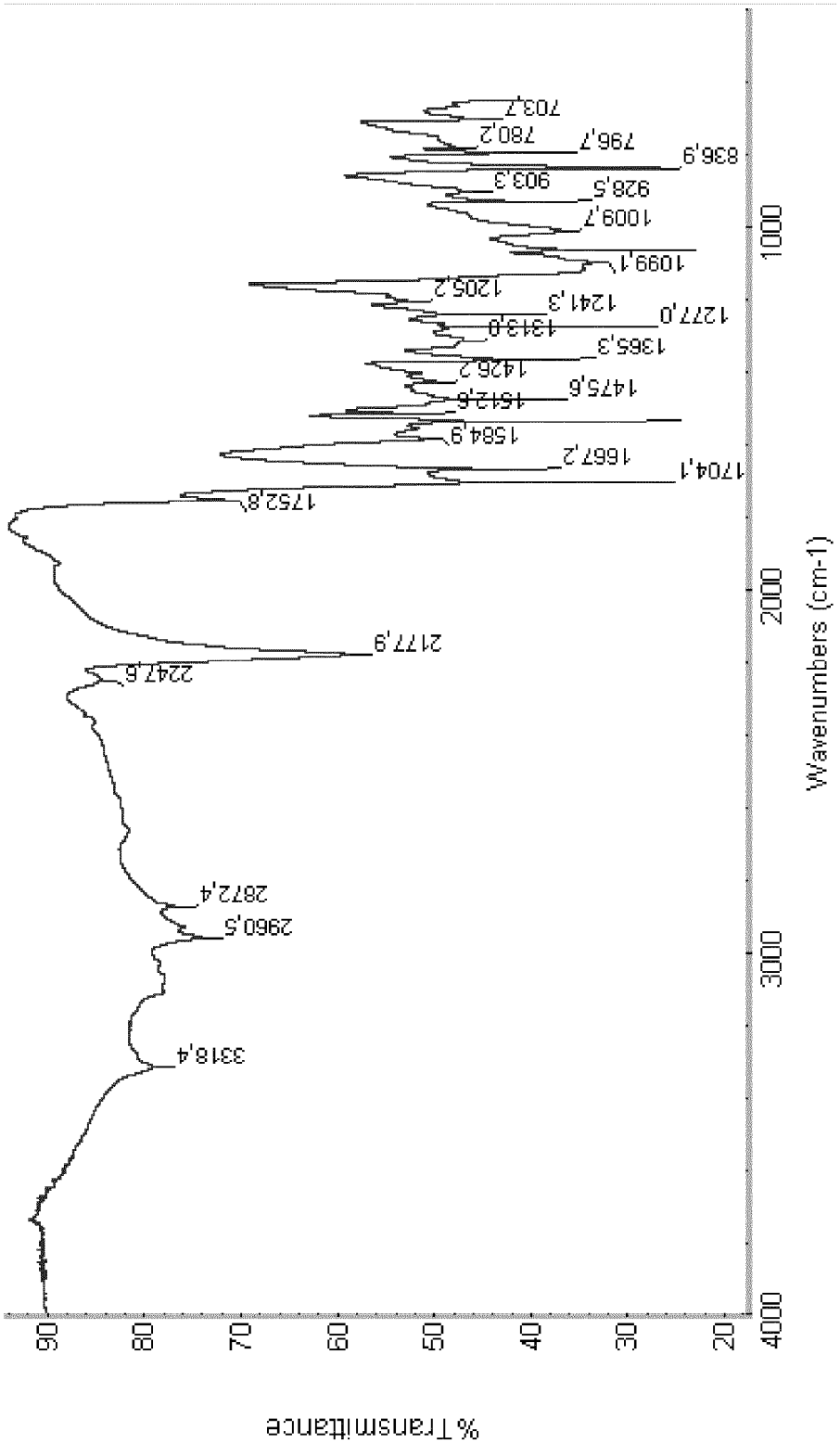


FIGURE 14 – FTIR of amorphous form



PRODRUG OF AN ANTI-INFLAMMATORY ACTIVE INGREDIENT

This application is a U.S. National Stage of PCT/EP2012/063414 filed Jul. 9, 2012, which claims priority to and the benefit of Italian Application No. MI2011A001288 filed Jul. 11, 2011, the contents of which applications are incorporated herein by reference in their entirety.

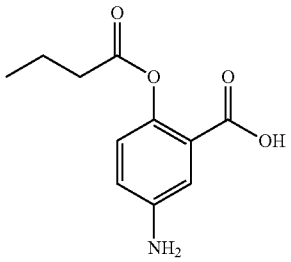
The present invention relates to a process for the preparation of a prodrug of 5-aminosalicylic acid, more particularly a process for the preparation of 2-butanoyloxy-5-amino-benzoic acid and solid forms of such compound.

The use of prodrugs of active ingredients is widespread in therapy. Prodrugs are derivatives of the active ingredient that show more favorable characteristics of bioavailability and once they reach their site of action they are metabolized into the active ingredient, exerting then an overall stronger pharmacological action than the active ingredient itself.

5-amino-salicylic acid or Mesalazine is a compound with anti-inflammatory activity widely used in the treatment of inflammatory diseases such as Crohn's disease and ulcerative colitis.

Among the possible prodrugs of such active ingredient those species wherein the phenolic group is esterified with carboxylic acids with medium chain, particularly with a butyryl group, are interesting.

The chemical structure of the butyric derivative, and more precisely of 2-butanoyloxy-5-amino-benzoic acid is represented by the following formula:

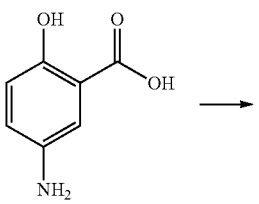


(I)

Derivatives of 5-aminosalicylic acid bearing an acyl on the phenolic group are known in literature and are generally prepared starting from 5-aminosalicylic acid by protection of the amino group, acylation of the phenolic group and subsequent amino deprotection. Such procedure becomes necessary because the direct acylation of 5-aminosalicylic acid leads to a double acylation of the substrate both on the amino and the phenolic group. By controlled deacylation, the N-monoacyl derivative but not the 0-monoacyl derivative can be obtained.

For example, WO2004000786 describes the preparation of the propanoyloxy derivative of 5-aminosalicylic acid through the following synthetic scheme:

Scheme 1



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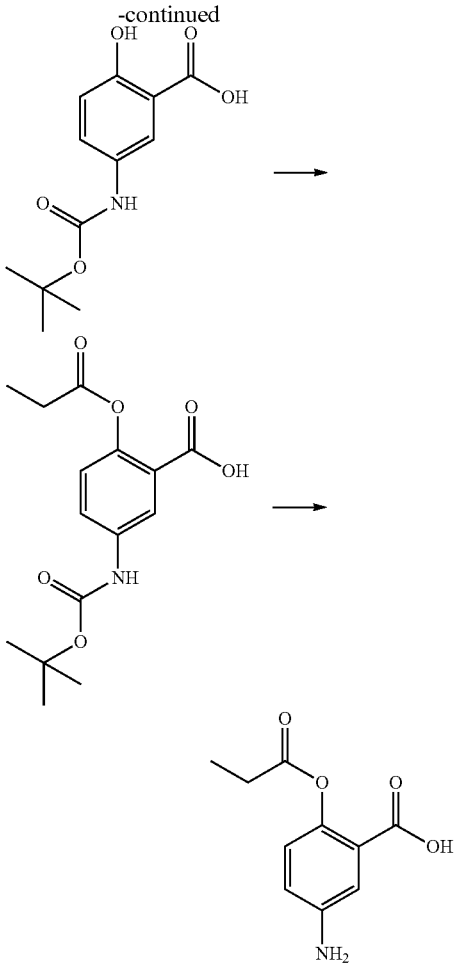


This method of synthesis results to be difficult and not particularly attractive from an industrial point of view.

We have now found that 2-butanoyloxy-5-amino-benzoic acid can be advantageously prepared through a process that avoids the problem of the protection and of the subsequent deprotection of the reactive functions of the molecule with the consequent reduction of the number of synthetic steps.

It is therefore object of the present invention a process for the synthesis of 2-butanoyloxy-5-amino-benzoic acid comprising the following steps:

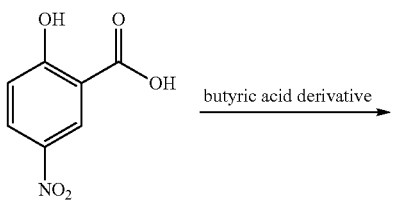
a) the acylation of 5-nitrosalicylic acid by reaction with a butyric acid reactive derivative, optionally in the presence of an acid catalyst;

b) the reduction of the nitro group;

c) the optional crystallization of the resultant product.

The synthetic process object of the present invention is reported in the following scheme:

Scheme 2



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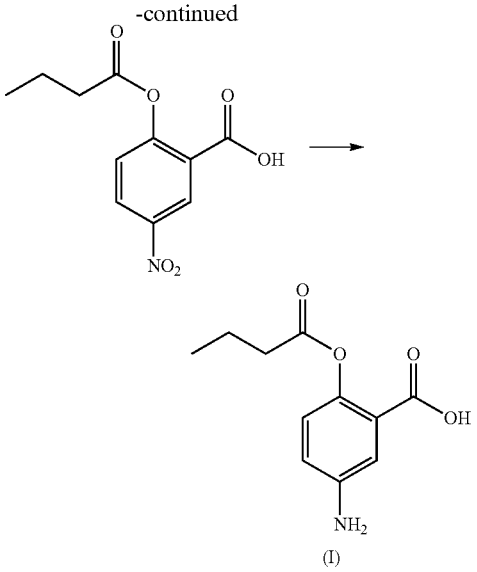

(I)

The first synthetic step of the process object of the present invention is carried out starting from 5-nitrosalicylic acid by reaction with a butyric acid reactive derivative, such as butyric anhydride or a butyryl halide, for example butyryl chloride or bromide.

Butyric anhydride is preferably used.

The reaction can be optionally carried out in the presence of an acid catalyst, such as for example methanesulfonic acid, p.toluenesulfonic acid, sulfuric acid or hydrogen halides.

Methanesulfonic acid is preferably used.

The acylation is carried out in a suitable organic solvent such as, for example, acetonitrile, dichloromethane or ethyl acetate.

The resultant 2-butanoyloxy-5-nitro-benzoic acid is reduced with conventional techniques obtaining the corresponding 5-amino derivative, preferably as a salt.

The reduction reaction of the nitro group is preferably carried out by catalytic hydrogenation in the presence of an inorganic acid.

The hydrogenation in the presence of catalytic amounts of Pd in a solution of hydrochloric acid in an organic solvent, for example dioxane, is particularly preferred.

To increase the purity of the resultant 2-butanoyloxy-5-amino-benzoic acid hydrochloride the crystallization of the product in a suitable solvent can be necessary.

We have found that 2-butanoyloxy-5-amino-benzoic acid hydrochloride can crystallize in different polymorphic forms.

Three crystalline forms of 2-butanoyloxy-5-amino-benzoic acid hydrochloride, named form I, form II and form III and an amorphous form were altogether characterized.

Such forms were characterized using PXRD (Powder X-Rays Diffraction), FTIR (Fourier Transform Infra Red), DSC (Differential Scanning Calorimetry) and TGA (Thermo Gravimetric Analysis) techniques.

The characterization of the crystalline forms I, II and III and of the amorphous form of 2-butanoyloxy-5-amino-benzoic acid hydrochloride was carried out using the following spectroscopic techniques, under the experimental conditions reported below:

PXRD (Powder X Ray Diffraction)

Experimental Conditions

Type of instrument: X'Pert PRO PANalytical

Type of measurement: Single scan

Wave lengths of measurement: Cu Kα1

Material constituting the anode: Cu

Voltage of the X-ray tube: 40

Power of the X-ray tube (mA): 40

Type of movement of the sample: Rotation

Rotation time of the sample (s): 1.0

Thickness of the filter (mm): 0.020

Filter material: Ni

Detector's name: X'Celerator

Type of detector: RTMS detector

Scan axis: Gonio

Scan range (°): 3.0000-39.9987

Width of the measurement range (°): 0.0167

Number of points: 2214

Scan mode: Continuous

Counting time (s): 12.700

Application software: X'Pert Data Collector vs. 2.2d

Control software of the instrument: XPERT-PRO vs. 1.9B

Temperature Room temperature

FT-IR (ATR)

Experimental Conditions

Type of instrument: Nicolet FT-IR 6700

ThermoFischer

Spectral range (Standard): 7800-350 cm^{-1}

Spectral range (Option, Csl Optics): 6400-200 cm^{-1}

Spectral range (Option, Extended-Range Optics): 11000-375 cm^{-1}

Spectral range (Option, Multi-Range Optics): 27000-15 cm^{-1}

Optical resolution: 0.09 cm^{-1}

Background noise peak to peak (1 min. scan): <8.68×10−6 AU*

Background noise RMS (1 minute scan): <1.95×10−6 AU*

Ordinate linearity: 0.07% T

Wavelength precision: 0.01 cm^{-1}

Minimum linear scan speed: 0.158 cm/sec

Maximum linear scan speed: 6.33 cm/sec

Number of scan speed: 15

Rapid scan (Spectra/second @16 cm^{-1}, 32 cm^{-1}): 65, 95

Number of scans of the sample: 32

Number of background scans: 32

Resolution: 4.000 cm^{-1}

Gain of the sample: 8.0

Optical speed: 0.6329

Opening: 100,00

Detector: DTGS KBr

Beam splitter: KBr

Source: IR

DSC

Experimental Conditions

Type of instrument: Perkin Elmer DSC-7

Calorimetric precision better than ±0.1%

Temperature precision ±0.1%

Temperature accuracy ±0.1%

Heating rate 10° C./min

Heating ramp from 30° C. to 250° C.

Sample preparation 1 mg in a 50μ perforated capsule

Thermal controller TAC 7/ΔX

TGA

Experimental Conditions

Type of instrument: STA 409 PC Luxx® Netzsch

Heating and cooling rate: 0.01 K/min . . . 50 K/min

TG resolution: up to 0.00002%

DSC resolution: <1 μW (K sensor)

DSC sensibilità: 8 μV/mW (K sensor)

Atmosphere: Inert (Nitrogen)

Gas flow control: 2 purge gases and 1 protective gas

Purge gas: Nitrogen
Purge gas speed: 60 ml/min
Protective gas: Nitrogen
Protective gas speed: 20 ml/min
Crucible: DSC/TG pan Al
Heating rate: 10° C./min
DSC Heating ramp: from 30° C. to 280° C.
TGA Heating ramp: from 40° C. to 500° C.

SHORT DESCRIPTION OF THE FIGURES

FIG. **1**—PXRD of form I
FIG. **2**—FTIR of form I
FIG. **3**—DSC of form I
FIG. **4**—TGA of form I
FIG. **5**—PXRD of form II
FIG. **6**—FTIR of form II
FIG. **7**—DSC of form II
FIG. **8**—TGA of form II
FIG. **9**—PXRD of form III
FIG. **10**—FTIR of form III
FIG. **11**—DSC of form III
FIG. **12**—TGA of form III
FIG. **13**—PXRD of amorphous form
FIG. **14**—FTIR of amorphous form

The crystalline form I of 2-butanoyloxy-5-amino-benzoic acid hydrochloride is an object of the present invention.

Form I according to the present invention has a PXRD with peaks at 4.7; 8.2; 9.5; 11.0; 11.7; 14.2; 16.5; 17.1; 20.7; 22.6; 24.5; 25.0; 29.0±0.20 2theta.

The form I of 2-butanoyloxy-5-amino-benzoic acid hydrochloride was characterized by PXRD, FTIR, DSC and TGA.

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.7494	3291.60	0.1171	18.60635	100.00
4.8826	2163.52	0.0669	18.09875	65.73
8.2085	570.39	0.1338	10.77151	17.33
9.4608	908.98	0.1338	9.34839	27.62
11.0346	234.62	0.1004	8.01839	7.13
11.7385	227.28	0.0669	7.53911	6.90
12.5274	87.79	0.1673	7.06603	2.67
14.2111	868.58	0.1506	6.23242	26.39
14.3169	560.63	0.0502	6.18661	17.03
15.3247	41.64	0.2342	5.78197	1.27
16.5077	204.19	0.2007	5.37017	6.20
17.0983	644.99	0.1673	5.18597	19.59
17.5040	80.39	0.1004	5.06668	2.44
18.1659	110.38	0.2342	4.88355	3.35
19.9127	44.85	0.1673	4.45891	1.36
20.6708	555.17	0.1004	4.29707	16.87
20.7770	410.19	0.0669	4.27535	12.46
21.5054	99.35	0.1338	4.13216	3.02
22.0251	136.41	0.1004	4.03581	4.14
22.6358	548.70	0.1673	3.92829	16.67
23.0698	140.21	0.1004	3.85536	4.26
23.7256	135.09	0.1171	3.75027	4.10
24.0648	78.58	0.1004	3.69817	2.39
24.5497	376.85	0.2007	3.62620	11.45
24.9596	647.66	0.0669	3.56758	19.68
26.3623	190.55	0.1171	3.38084	5.79
26.7412	123.54	0.1004	3.33379	3.75
27.3096	38.94	0.1338	3.26569	1.18
27.6395	86.08	0.1338	3.22746	2.62
28.0423	21.29	0.1338	3.18200	0.65
28.4646	264.37	0.1338	3.13575	8.03
29.0116	453.88	0.1506	3.07786	13.79
29.7970	153.73	0.1673	2.99850	4.67
31.5868	71.04	0.2342	2.83257	2.16
32.3257	201.69	0.1338	2.76948	6.13

-continued

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
33.1705	88.95	0.1338	2.70086	2.70
33.4710	130.88	0.1673	2.67729	3.98
34.4577	153.06	0.1020	2.60070	4.65
34.5804	153.82	0.0836	2.59390	4.67
34.9696	57.45	0.2007	2.56591	1.75
35.4372	35.39	0.1338	2.53313	1.08
36.3873	112.55	0.2007	2.46914	3.42
37.0786	27.91	0.1338	2.42467	0.85
37.4940	37.63	0.1673	2.39876	1.14
38.0974	133.58	0.2007	2.36214	4.06
39.3147	57.63	0.1004	2.29177	1.75

The profile of the diffractogram of form I is reported in FIG. **1**.

FTIR—the FTIR profile of form I is reported in FIG. **2**.

DSC—the profile related to form I is reported in FIG. **3**. It shows an onset at 142.5° C.

TGA—the TGA profile related to form I is reported in FIG. **4**.

The form I of 2-butanoyloxy-5-amino-benzoic acid hydrochloride can be prepared by crystallization of 2-butanoyloxy-5-amino-benzoic acid hydrochloride from toluene and acetone. The crystallization is preferably carried out by dissolving 2-butanoyloxy-5-amino-benzoic acid hydrochloride in toluene at a temperature between room temperature and 70° C., preferably between 30° C. and 50° C., and then by adding acetone. By cooling of the solution, preferably at room temperature a suspension is formed from which the crystalline form I is isolated by filtration, washing and drying.

Crystalline form II of 2-butanoyloxy-5-amino-benzoic acid hydrochloride is an object of the present invention.

Form II according to the present invention has a PXRD with peaks at 10.9; 11.6; 15.2; 16.1; 18.2; 20.8; 21.4; 21.9; 22.5; 23.3; 23.7; 24.5; 25.0; 26.7; 27.2±0.20 2theta.

The form II of 2-butanoyloxy-5-amino-benzoic acid hydrochloride was characterized by PXRD, FTIR, DSC and TGA.

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
10.5768	475.72	0.0669	8.36441	7.31
10.9220	2476.66	0.1171	8.10080	38.03
11.6337	5247.96	0.1004	7.60677	80.59
12.1300	358.24	0.0836	7.29664	5.50
13.2907	318.25	0.1171	6.66188	4.89
15.1965	551.37	0.1171	5.83045	8.47
16.1404	1429.54	0.1506	5.49154	21.95
16.8495	30.39	0.2007	5.26199	0.47
18.2465	647.88	0.1338	4.86215	9.95
18.9985	140.77	0.1004	4.67137	2.16
19.2829	51.36	0.1004	4.60310	0.79
19.8734	287.51	0.1338	4.46764	4.42
20.7663	1279.08	0.1338	4.27751	19.64
21.1909	508.15	0.0502	4.19275	7.80
21.4180	1603.79	0.1338	4.14882	24.63
21.8717	1265.18	0.1338	4.06377	19.43
22.5215	3056.67	0.1506	3.94797	46.94
23.2973	987.32	0.1506	3.81822	15.16
23.6507	2628.10	0.1338	3.76198	40.36
24.4767	6511.66	0.1673	3.63686	100.00
25.0432	1983.44	0.1673	3.55586	30.46
25.5100	163.32	0.1004	3.49184	2.51
26.2111	454.22	0.1506	3.40001	6.98

-continued

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
26.6562	2648.36	0.1673	3.34423	40.67
27.1982	1101.18	0.1673	3.27881	16.91
27.5733	273.93	0.0836	3.23506	4.21
28.7092	557.74	0.1338	3.10959	8.57
29.3891	794.68	0.1506	3.03918	12.20
29.8867	196.75	0.0836	2.98970	3.02
31.2908	736.24	0.1840	2.85868	11.31
31.9773	492.59	0.1673	2.79886	7.56
32.4540	430.54	0.1171	2.75883	6.61
33.0666	570.26	0.1673	2.70910	8.76
33.5393	146.62	0.1338	2.67200	2.25
33.7299	148.82	0.1338	2.65733	2.29
34.2216	68.59	0.1338	2.62027	1.05
34.8428	852.67	0.1673	2.57496	13.09
35.3379	13.31	0.1338	2.54001	0.20
35.6993	57.78	0.1338	2.51513	0.89
36.4753	269.57	0.2007	2.46338	4.14
37.3876	89.31	0.0502	2.40534	1.37
37.8926	250.71	0.1004	2.37444	3.85
38.1350	525.65	0.1004	2.35990	8.07
38.4503	286.00	0.0836	2.34127	4.39
39.1109	125.92	0.1338	2.30323	1.93
39.6235	168.51	0.1338	2.27461	2.59

The profile of the diffractogram of form II is reported in FIG. **5**.

FTIR—the FTIR profile of form II is reported in FIG. **6**.

DSC—the profile related to form II is reported in FIG. **7**. It shows an onset at 154.8° C.

TGA—the TGA profile related to form II is reported in FIG. **8**.

The form II of 2-butanoyloxy-5-amino-benzoic acid hydrochloride can be prepared by conversion of form I.

The preparation of form II is preferably carried out by suspending 2-butanoyloxy-5-amino-benzoic acid hydrochloride form I in an organic solvent selected among methyl-t-butyl ether, dimethoxyethane, diethylether, dioxane, isopropylether, anisole, dichloromethane, chloroform, ethyl formate, propylacetate, ethylacetate, methylacetate, diethyl carbonate, acetonitrile, benzonitrile, nitromethane, cyclopentanone, 3-pentanone and acetone at a temperature around room temperature and maintaining the suspension at such temperature for several hours. Form II is then obtained by filtration of the suspension.

Alternatively, the conversion of form I into form II can be carried out by maintaining form I under an atmosphere of controlled humidity for several hours at a temperature around room temperature.

The water content in the form II object of the present invention is about 0.4-0.5%.

Crystalline form III of 2-butanoyloxy-5-amino-benzoic acid hydrochloride is an object of the present invention.

Form III according to the present invention has a PXRD with peaks at 3.6; 7.1; 10.6; 14.2±0.20 2theta.

The form III of 2-butanoyloxy-5-amino-benzoic acid hydrochloride was characterized by PXRD, FTIR, DSC and TGA.

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.6347	2587.49	0.1338	24.30926	86.59
7.1396	2988.27	0.1673	12.38173	100.00
9.0279	30.10	0.4015	9.79566	1.01

-continued

PXRD - Positions and characteristics of the relevant peaks (uncertainty range on the position of the peak ±0.20 2theta)

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
10.6479	268.52	0.1673	8.30867	8.99
12.6230	59.07	0.2007	7.01272	1.98
14.1753	533.95	0.1840	6.24810	17.87
15.7155	144.52	0.1004	5.63905	4.84
16.5365	91.47	0.3346	5.36088	3.06
18.7841	120.21	0.4015	4.72419	4.02
19.6032	20.25	0.2676	4.52861	0.68
20.2273	13.91	0.2007	4.39026	0.47
20.8639	111.67	0.1673	4.25773	3.74
21.2880	174.67	0.1004	4.17386	5.85
22.0406	70.97	0.1673	4.03301	2.37
22.5229	38.96	0.2007	3.94773	1.30
23.1599	46.20	0.1338	3.84057	1.55
24.0391	112.21	0.1338	3.70207	3.76
24.8095	31.56	0.2007	3.58882	1.06
25.3720	69.40	0.1338	3.51051	2.32
25.7851	145.59	0.1338	3.45521	4.87
26.2812	60.79	0.2007	3.39110	2.03
27.2727	48.14	0.2007	3.27003	1.61
28.0575	107.41	0.1338	3.18031	3.59
28.6040	78.04	0.1004	3.12079	2.61
29.3231	24.12	0.3346	3.04588	0.81
31.3670	60.22	0.2676	2.85191	2.02
31.9768	62.35	0.2007	2.79890	2.09
34.2012	27.44	0.3346	2.62178	0.92
35.0471	42.99	0.1338	2.56042	1.44
38.7343	19.20	0.4015	2.32476	0.64

The profile of the diffractogram of form III is reported in FIG. **9**.

FTIR—the FTIR profile of form III is reported in FIG. **10**.

DSC—the profile related to form III is reported in FIG. **11**. It does not show fusion peaks.

TGA—the TGA profile related to form III is reported in FIG. **12**.

The form III of 2-butanoyloxy-5-amino-benzoic acid hydrochloride can be prepared by conversion of form I.

The preparation of form III is preferably carried out starting from 2-butanoyloxy-5-amino-benzoic acid hydrochloride form I by crystallization from a solvent selected among isopropanol, isobutanol and acetone. The crystallization is preferably carried out by dissolving form I in a solvent and leaving the solution evaporating at a temperature around room temperature up to obtain a crystalline solid.

The amorphous form of 2-butanoyloxy-5-amino-benzoic acid hydrochloride is an object of the present invention.

The amorphous form was characterized by PXRD and FTIR.

PXRD—the profile of the diffractogram does not show defined diffraction peaks as occurs for amorphous products.

The profile of the diffractogram of the amorphous form is reported in FIG. **13**.

FTIR—the FTIR profile of the amorphous form is reported in FIG. **14**.

In order to better illustrate the present invention, without however limiting it, the following examples are now given.

Example 1

Preparation of 2-butanoyloxy-5-nitro-benzoic acid

50 g of 5-nitrosalycilic acid, 50 ml of acetonitrile, 111.7 ml of butyric anhydride and 0.18 ml of methanesulfonic acid were loaded into a 500 ml reactor under nitrogen atmosphere. The mixture was heated under stirring to 80±2° C. up to obtain a complete dissolution. The mixture was maintained at 76±2° C. for 2 hours, then cooled to 25° C. in about two hours

and kept under stirring for 16 hours. At the end the solvent was evaporated at 40° C. under vacuum and the residual was added with 70 ml of dichloromethane. 500 ml of heptane were then added in one hour to the resultant solution. A precipitate formed in suspension, that was kept under stirring at room temperature for one hour and for one hour at 0° C., for being then filtered on a buckner and washed with two aliquots of 70 ml of heptane. The solid was dried at 35° C. under vacuum (30 mmHg) for two hours giving 35 g of the expected product (51% yield).

Example 2

Preparation of crude 2-butanoyloxy-5-amino-benzoic acid hydrochloride

10 g of 2-butanoyloxy-5-nitro-benzoic acid, 8.5 ml of dioxane, 1.5 ml of HCl 4M solution in dioxane and 1.0 g of Pd/C at 5% were loaded into a 300 ml reactor at 16±2° C. After two vacuum-nitrogen cycles, the reactor was saturated with hydrogen at 10 bar and kept at 16±2° C. for 6 hours. At the end, nitrogen atmosphere was restored in the reactor and the reaction mixture was added with 125 ml of acetone at 25° C. The suspension was stirred at 25° C. for 30 minutes to obtain the dissolution of the undissolved product and the carbon suspension was filtered on a celite panel which was then washed with 60 ml of acetone. The resultant solution was then evaporated under vacuum at 30° C. and the solid residue was dried under vacuum at 35° C. for 4 hours to obtain 10 g of the expected product (99% yield).

Example 3

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I

10 g of crude 2-butanoyloxy-5-amino-benzoic acid hydrochloride and 40 ml of toluene were loaded into a 250 ml reactor. The suspension was heated up to 40° C. and 90 ml of acetone were added at such temperature obtaining a solution. 25 ml of toluene were then added to the mixture obtaining a slightly cloudy of the mixture. The mixture was cooled to 25±2° C. in two hours and subsequently at 0±2° C. in 30 minutes, and kept at such temperature for one hour. The resultant suspension was filtered on a buckner and washed with two aliquots of 15 ml of toluene. The wet solid was dried under vacuum at 35° C. for 6 hours, obtaining 5.5 g of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I.

Example 4

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form II

50 mg of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I, prepared as described in example 3, were suspended in 2 ml of isopropyl acetate and kept under such conditions at room temperature for 7 days. At the end the product was filtered and analyzed. PXRD showed that the crystalline form of the resultant product was the form II.

Example 5

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form II

By working in a similar manner as described in example 4, but using as dispersing medium, for each experiment, one of the following solvents: methyl-t-butyl ether, dimethoxyethane, diethylether, dioxane, isopropylether, anisole, dichloromethane, chloroform, ethyl formate, propylacetate, ethylacetate, methylacetate, diethylcarbonate, acetonitrile, benzonitrile, nitromethane, cyclopentanone, 3-pentanone and acetone, a crystalline solid which resulted to be the form II was obtained.

Example 6

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form II

1.0 g of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I, prepared as described in example 3, were introduced in a laboratory dryer in which lower portion a saturated K_2CO_3 solution was prepared. The temperature was kept constant at 20° C. to obtain a relative humidity of about 43% inside the dryer. After 24 hours a sample was removed and the crystalline form was analyzed by X ray. PXRD showed that the crystalline form of the resultant product was the form II. The water content of the sample increased from an initial value of 0.3% up to a final value of 0.42%.

Example 7

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form II

1.0 g of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I, prepared as described in example 3, were introduced in a laboratory dryer in which lower portion a saturated NaCl solution was prepared. The temperature was kept constant at 20° C. to obtain a relative humidity of about 75% inside the dryer. After 24 hours a sample was removed and the crystalline form was analyzed by X ray. PXRD showed that the crystalline form of the resultant product was the form II. The water content of the sample increased from an initial value of 0.3% up to a final value of 0.49%.

Example 8

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form III

50 mg of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I, prepared as described in example 3, were dissolved in 4 ml of isopropanol, filtered on a 0.45μ Whatman filter and the resultant solution was left to spontaneously evaporate at 4° C. for 7 days. The resultant solid was then analyzed. PXRD showed that the crystalline form of the resultant product was the form III.

Example 9

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form III

By working in a similar manner as described in example 8 but using as solvent medium, for each experiment, a solvent selected among acetone and isobutanol, a crystalline solid was obtained which resulted to be the form III.

Example 10

Preparation of 2-butanoyloxy-5-amino-benzoic acid hydrochloride amorphous form

50 mg of 2-butanoyloxy-5-amino-benzoic acid hydrochloride crystalline form I, prepared as described in example 3,

were dissolved in 4 ml of dichloromethane, filtered on a 0.45μ Whatman filter and the resultant solution was left to spontaneously evaporate at room temperature (25° C.) for 3 days. The resultant solid was then analyzed. PXRD showed that the crystalline form of the resultant product was amorphous.

The invention claimed is:

1. Crystalline Form I of 2-butanoyloxy-5-amino-benzoic acid hydrochloride characterized by a PXRD with peaks at 4.7; 8.2; 9.5; 11.0; 11.7; 14.2; 16.5; 17.1; 20.7; 22.6; 24.5; 25.0; 29.0±0.20 2theta.

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